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NUTRITION REVIEWS

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NUTRITION REVIEWS

VOL. 12 OCTOBER 1954 No. 10

FOOD FORTIFICATION IN THE ORIENT

The appearance of an FAO (Food and Agriculture Organization) report on "Rice Enrichment in the Philippines" (*FAO Nutritional Studies No. 12, Rome, Italy (1954)*) has followed closely on the heels of a report of the Indian Council of Medical Research entitled "Fortification of Foods." These two reports can well be discussed jointly, as both largely reflect a somewhat typical European-Asian or perhaps Anglo-Indian prejudice against artificial re-enforcements of foods as solutions to deficiency problems.

The FAO team in the Philippines had broadly two questions to answer: (1) Has rice fortification (enrichment) been effective where it has been applied? (2) Is it capable of extension to larger populations? Several other questions concerning the validity of diagnoses of beriberi in the Philippines, the possible applicability of other measures for its eradication, etc., were of course involved.

It is unfortunate for a full answer to question 1 that, through no fault of the team, its visit occurred two years after the Bataan Experiment (J. Salcedo *et al., J. Nutrition* **42,** *501 (1950)*; *Nutrition Reviews* **9,** *218 (1951)*) was concluded. It is doubly unfortunate that, lacking the opportunity to see the experiment in progress, the team, possibly influenced unfavorably by the poor progress made in extending enrichment to other areas of the Philippines, apparently assumed that these shortcomings had also applied to the experimental area and period.

A failure of the report to evaluate the evidence objectively is its presentation of only "selected" statistical information. Table II on page 12 of the report gives death rates from beriberi in two columns headed "Manila" and "Philippines" respectively. Actually, mortality figures for beriberi over a long period were made available to the team for each of the 49 provinces (*Philippine Nutrition News* **7,** *No. 3 (1954)*), as well as Manila before the report was published. Each province has its own Health Officer who makes an independent report for his province. Each of these reports has equal validity in absence of evidence to the contrary and they jointly cover 90 per cent of the population. By publishing the team's choice of only two columns out of an available fifty the picture was grossly distorted.

An even greater disregard of scientific objectivity was displayed on page 37 in the following words: ". . . it was considered desirable to study the trend in beriberi mortality rates during the corresponding period in a nearby Province into which no enriched rice had as yet been introduced. Such a Province was Tarlac . . ." The fact is that Tarlac was *not* such a province, for enriched rice had been introduced there in significant amounts (1400 metric tons) by January, 1951, and by the end of June, 1951, premix for 2500 metric tons of enriched rice had been supplied to Tarlac through 215 of its rice mills which had already been equipped for the purpose. The team might fairly have chosen any one of 47 other provinces to compare with Bataan, for enriched rice had not gone to them. Instead, they chose Tarlac, the only province besides Bataan where enriched rice had already entered one and one-half years before. Hence, the implication in Table VIII, page 40, that beriberi was declining generally in the Philippines at the time of the Bataan Experiment is sheer fiction. Actually, Table VIII merely shows how much Tarlac also had benefitted from rice enrichment.

Actually, subsequent data clearly show that lowering of beriberi mortality has been surprisingly well maintained in Bataan,

Tarlac and Pangasinan through 1952 and 1953 in spite of the fact that the extent of enrichment during these years in these three provinces has been only 5 to 10 per cent of the total rice supply. This can be accounted for only on the assumption that when enriched rice is available on the market it is preferentially sought and used by families with past experience of beriberi. The fall in beriberi mortality is thus out of proportion to the percentage of the rice supply enriched. Other provinces of the Philippines to which enrichment has not been extended at all do not show these drops in beriberi mortality.

When the Bataan Experiment was planned, a major safeguard against faulty conclusions was the establishment of a control area within the Province of Bataan. Enriched rice was made available only to the experimental area of the province and unenriched rice continued to be eaten in the control area. During the course of the experiment the continuing mortality from beriberi in the control area, in contrast to the drop in such mortality in the experimental area, made the conclusion inescapable that the enrichment of rice was exclusively responsible for the reduction in the beriberi death rate. But the FAO report makes no mention whatever of the control area and its undiminished mortality rate on an unenriched rice diet.

Knowing the full facts of the case, the only conclusion one can draw from the FAO report is that the team as a whole or some of its members did not examine the evidence objectively. This does not represent a hopeful situation for the people of Asia. Some of the food problems of certain Asian countries seem almost insuperable even with the best applications of science. Failure to take note of the very real promise of rice enrichment for certain areas can hardly be recognized as a scientific contribution to the welfare of Asians.

As to question 2, concerning the possibility of extending rice enrichment to larger populations, the FAO report is more factual. It is true that extension of rice enrichment on a commercial, nonsubsidized basis has not yet proven successful in the Philippines. Yet all of the obstacles to success which are mentioned in "General Comments and Conclusions" on page 67 are of quite minor consequence compared with one not mentioned, viz., the lack, so far, of effective coordination on the part of all departments of the Philippine government to enforce the rice enrichment law. A comprehensive Executive Order signed by President Magsaysay on August 23, 1954, now for the first time provides for a widespread and systematic distribution of premix and prescribes a schedule for the introduction of rice enrichment in every city and province of the Philippines during 1955 and 1956. Had the FAO report appeared earlier it might have defeated all efforts to achieve this action.

"Fortification of Foods," published by the Indian Council of Medical Research (*Special Report Series No. 27, New Delhi (1953)*) is a companion piece as a subject of psychologic study. This report has value as a factual study only if the reader has at hand accurate information to supplant the misinformation throughout the text. On pages 4 and 5, for instance, a completely distorted picture is given of food fortification in the United States. Contrary to the statement in this report, fortification of carbonated beverages is *not* sanctioned by federal law and there is little such fortification in interstate commerce. It is more frequent, but still rare, in the case of beverages locally produced and locally sold. Further, and again opposed to this report's statements, most of the fortifications of foods for the American armed forces are limited to certain emergency or stress rations. The only fortified food which either field or garrison soldiers regularly receive is white flour.

In the same passage reference to Newfoundland is made which, it is alleged, has "not apparently yielded any *convincing* evidence in favor of or against fortification" (my italics). How can one reconcile this statement with the conclusions of the authors

of the second Newfoundland Survey (W. R. Aykroyd *et al.*, *Canad. Med. Assn. J.* **60,** *329 (1949)*; *Nutrition Reviews* **7,** *331 (1949)*), as follows? ". . . those signs and symptoms which could have been expected to decrease in prevalence as a result of fortification of margarine with vitamin A and the enrichment of flour with riboflavin, niacin and thiamine were less frequently encountered and less severe in 1948 than 1944, whereas the prevalence of lesions which could not have been affected by these measures remained unaltered or actually increased." Perhaps the writers of the Indian report felt that they could judge the results better at a distance than the observers on the ground. Perhaps the key word in the Indian statement is the word "convincing." One is reminded of the adage, "He who is convinced against his will, is of the same opinion still."

Another such passage appears on page 9 of the report: ". . . the U. S. A. where the problem perhaps is to find the market for synthetic and other nutrients . . ." casts gratuitous aspersions on the integrity of our national Food and Nutrition Board which sponsored all the fortifications which have been so widely adopted. It is well known in America that vitamin production was insufficient to meet the need fully for three years after the policy was adopted.

A complete lack of grasp of the philosophy of cereal enrichment is found in the central paragraph on page 12: The statement "The only alternative which appears practicable is to leave the actual enrichment to the consumer" is an incredible absurdity. Practical experience in trying to change dietary habits shows that unless cereal enrichment is made universal with respect to major staples, either by industry action or by government action, it may as well be abandoned. Any lesser action will have no more value than the simpler process of telling the people to take pills or to choose their food with scientific skill. The low income masses, who are the ones most in need of nutritional supplements, will not actually follow such advice.

Perhaps the most glaring instance of misinformation in the Indian report is in the appendix which lists in detail the fortification standards for 15 food products in the United States and elsewhere. Of the 15 standards it attributes to the United States, 11 do not exist either as legal standards or as common practices in commerce. Contrary to the report's statement, the only fortification or enrichment standards in the United States are those for white flour, white bread, corn meal or grits, alimentary pastes, oleomargarine (with vitamin A), milk (with vitamin D), and table salt (with iodine).

Shortage of dollars or other hard currency, rather than any of the other reasons given in the Indian report, will act to limit the potential of food enrichment in Asian countries, except as Asia can expand her exports to the West or manufacture the vitamins for herself. Further enrichment by present formulas will not help to solve two of India's major food problems, viz., shortage of total calories and shortage of good quality proteins. There are, however, various areas in Asia where cereal enrichment can be made to work for public welfare more economically and more quickly than any other available measure. There are other areas where it is impracticable or where it would be less effective, and these areas include much of India. India's adaptation of the general idea to her needs must be gradual and perhaps regional at first.

The Summary and Recommendations on pages 18–19 reflect a rather surprising optimism about the usefulness of enrichment in India. One doubts that the Committee appreciates the magnitude of the tasks it rather casually recommends. What purpose then was to be served by the disparagements of endeavors elsewhere which have been cited above? Perhaps the inconsistency of text and conclusions merely reflects a residual conflict of opinion within the Committee.

ROBERT R. WILLIAMS, *Chairman*
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SODIUM RESTRICTION AND CIRCULATORY DYNAMICS IN CIRRHOSIS

One of the commonest complications of cirrhosis of the liver is ascites formation. Rapid reaccumulation of ascites requires paracentesis (needle puncture for removal of fluid), and frequent paracenteses deplete the body not only of water and electrolytes, but also of plasma proteins and perhaps other nutrients—so much so that it seems to be one of the causes of the severe chronic undernutrition generally observed in chronic cirrhosis. Several investigators have demonstrated that ascites formation can be controlled by rigid dietary sodium restriction (*Nutrition Reviews* **9,** *278 (1951)*; **10,** *130 (1952)*). The importance of this with respect to the nutritional rehabilitation of the patient with chronic cirrhosis cannot be underestimated.

Continuing their studies of the relation of sodium restriction to ascites formation, G. J. Gabuzda, H. S. Traeger, and C. S. Davidson (*J. Clin. Invest.* **33,** *780 (1954)*) studied the effect of sodium ingestion and withdrawal and of paracentesis upon fluid and electrolyte balance in 7 patients with cirrhosis of the liver suffering from ascites. They found a direct relation between the quantity of sodium ingested and the rate of ascites formation, fluid being retained approximately isotonically.

Several of the patients observed by these investigators developed gradually progressive reductions in hematocrit and increases in serum sodium concentration which were followed, usually, first by water and then by gradual sodium and water diuresis with loss of remaining ascites and edema. When these changes occurred after prolonged dietary sodium restriction there was also an improvement in nutritional status and usually also in plasma albumin concentration. This was attributed by the authors to improvement in liver function.

Immediately following paracentesis the evidence of a rising hematocrit, rapidly expanding ascites, decreased peripheral edema, and reduction in urine volume indicated a rapid transudation of fluid from the plasma into the peritoneal cavity and a mobilization of edema fluid as well. It is not surprising then that peripheral vascular collapse is sometimes observed in this circumstance and that there may be a temporary slight increase in the cardiac output as found by H. J. Kowalski, W. H. Abelmann, and W. F. McNeely (*J. Clin. Invest.* **33,** *768 (1954)*). Gabuzda and his colleagues also found that repeated paracentesis sometimes resulted in a chronic state of dehydration and postulated that this might account for the appearance of increased diuretic activity and for the renal conservation of sodium in these patients.

Although Kowalski and his colleagues found a few patients with a rise in cardiac output immediately after paracentesis, it was not sustained, there being a rather prompt return to the original level. Kowalski and Abelmann (*J. Clin. Invest.* **32,** *1025 (1953)*) had previously found an elevated cardiac output in many of the patients with cirrhosis of the liver they studied. The cause of the high cardiac output found by these investigators has not been determined, although arteriovenous shunts within the liver, a metabolic deficiency of thiamine as cocarboxylase, or some other cause for the reduced peripheral resistance associated with the high output were postulated.

In summary, the cardiac output in cirrhosis of the liver is frequently high, and may rise slightly immediately after paracentesis, at a time when hemoconcentration occurs. Rigid dietary restriction of sodium will prevent the reaccumulation of ascites and edema in patients with cirrhosis of the liver. Prolonged dietary sodium restriction is often associated with striking improvement in nutritional status, a rise in serum albumin, improvement in liver function tests, a return to normal of the serum sodium and further loss of fluid accumulations.

AN EFFECT OF VITAMIN B_{12} AND FOLACIN ON THE NUCLEIC ACID CONTENT OF BONE MARROW

The therapeutic effectiveness of vitamin B_{12} and of folacin in various forms of megaloblastic anemia has been demonstrated (*Nutrition Reviews* **7,** *146, 261 (1949)*; **8,** *165 (1950)*). These nutrients have become important additions to the group of substances utilized in the treatment of anemia. The types of anemia responding to this approach in therapy are all characterized by an arrest in maturation of developing red blood cells in the bone marrow. It is reasonable to assume, therefore, that vitamin B_{12} and folacin must mediate their effect through an influence upon systems of metabolism which are integral to the development of red blood cells.

Other evidence has indicated that vitamin B_{12} and folacin have metabolic roles in the synthesis of nucleic acids or more specifically are involved in the metabolism of purines and pyrimidines (*Nutrition Reviews* **7,** *19 (1949)*; **9,** *185 (1951)*).

In a recently published study an attempt was made to determine the effect of vitamin B_{12} and folacin on the nucleic acid content of the bone marrow of patients with pernicious anemia or other types of megaloblastic anemia (H. S. Glazer and co-workers, *J. Lab. Clin. Med.* **43,** *905 (1954)*). Specimens of bone marrow were obtained by aspiration from the sternum or iliac crest of 29 patients. The material obtained was examined histologically and by chemical analysis. Ribonucleic acid (RNA) and desoxyribonucleic acid (DNA) were determined by use of the color reactions with orcinol and diphenylamine. Purine and pyrimidine bases were isolated by procedures of paper chromatography and then determined spectrophotometrically. The investigators did not relate values to unit weight of the specimens or to other cell constituents as standards of reference. Rather, values are expressed in ratios. Nucleic acids are recorded as the ratio of RNA to DNA. Purines and pyrimidines are given as ratios of uracil to thymine and thymine to total bases.

It was found that in 17 patients who had had previous manifestations of megaloblastic anemia but who were normal hematologically at the time of bone marrow examination there was a mean ratio of RNA to DNA of 0.316. This group was taken as a control group. The ratio RNA/DNA was uniformly higher in the bone marrow of 12 other patients in active phases of megaloblastic anemia. The mean value prior to treatment was 0.835.

Similarly, the ratio of uracil to thymine was increased in the bone marrow of patients with untreated megaloblastic anemia. The mean value of this ratio in the control group was 0.133, which compared with 0.316 in the group of patients with hematologic evidence of anemia. Also, in this latter group there was a decrease in the per cent thymine in the total purine and pyrimidine bases.

Treatment of these patients with either vitamin B_{12} or folacin was followed by evidence of correction of the anemia. There was an increase in the number of red blood cells, a decrease in the per cent of megaloblasts in the bone marrow, and an increase in circulating reticulocytes. Concurrent with and often preceding these evidences of hematologic response there were changes in the nucleic acids in the bone marrow. The RNA/DNA and the ratio of uracil to thymine decreased and the percentage thymine in the total bases increased. Each of these ratios was within the normal or control range when the hematologic defect had been fully corrected.

These clinical observations add support to the concept that vitamin B_{12} and folacin influence nucleic acid metabolism. The most important effect in bone marrow would seem to be on the RNA. However, the data recorded demonstrate an increase in the ratio of RNA to DNA in megaloblastic anemia.

Since the total quantity of these nucleic acids per cell was not determined, it is not possible to state whether the increased ratio results from increased quantities of RNA or decreased DNA content of bone marrow. In addition, the quantitative changes in the cellular concentration of purine and pyrimidine bases are unexplained, although it is apparent that there is relatively more uracil as compared to thymine or total bases in the bone marrow of patients with pernicious anemia in relapse. It should be recalled that thymine, a component of DNA, is importantly influenced in its metabolism by folacin and vitamin B_{12}. The authors feel that their observations are consistent with the hypothesis that, in hematopoietic tissues, folacin and vitamin B_{12} initiate chemical reactions which favor the formation of thymine and its desoxyribotides and the depletion of uracil and its nucleotides.

It is interesting to note that it had been observed previously in the same laboratory through cytochemical studies of bone marrow that the RNA of the erythroblast of patients with pernicious anemia changes after administration of vitamin B_{12} or folacin, becoming less granular (D. Horrigan, T. Jarrold, and R. W. Vilter, *J. Clin. Invest.* **30,** *31 (1951)*). Other investigators have found that the quantities of RNA and DNA phosphorus of cells in the bone marrow of patients with pernicious anemia in relapse are increased, and decrease when the hematopoietic vitamins are given in treatment (J. N. Davidson, I. Leslie, and J. C. White, *Lancet* **I,** *1287 (1951)*; M. L. Menten and M. Willms, *Arch. Path.* **54,** *351 (1952)*). The decrease in RNA phosphorus was relatively less than that in DNA phosphorus, which would account for changes in RNA/DNA similar to those observed by Glazer and her associates (*loc. cit.*).

These investigations are of particular significance because they not only add to the fundamental understanding of the modes of action of folacin and vitamin B_{12} but afford new information concerning the defect in metabolism of cells in the bone marrow associated with pernicious anemia and other forms of megaloblastic anemia.

HEPARIN AND THE LIPEMIA CLEARING REACTION

During the last four years great interest has centered around the plasma lipoproteins and, in particular, their possible role in the genesis of atherosclerosis (J. W. Gofman and co-workers, *Science* **111,** *166 (1950)*; *Nutrition Reviews* **9,** *167 (1951)*). Certain classes of these lipoproteins, namely aggregates with flotation rates of 10 to 20 S_f units, have been especially implicated in the genesis of atherosclerosis. It may become of considerable clinical importance to be able to alter the plasma lipoprotein pattern in order to minimize atherogenesis. Heparin is capable of clearing lipemic plasma and of altering the lipoprotein pattern.

Heparin is a complex carbohydrate containing mucoitin-sulfuric acid esters. It was isolated from liver by W. H. Howell and E. Holt (*Am. J. Physiol.* **47,** *328 (1918)*) after J. McLean (*Ibid.* **41,** *250 (1916)*), a pupil of Howell, had discovered that crude liver extracts inhibited the coagulation of blood. Since these discoveries and the development of dependable commercial preparative technics, extensive clinical application of heparin has been made.

P. F. Hahn (*Science* **98,** *19 (1943)*), in the course of his studies on the red cell circulating mass in dogs, discovered that the lipemic plasma of animals which received heparinized blood was cleared in three to five minutes. He also showed that heparin injections alone cleared lipemic plasma. Addition of heparin *in vitro* to lipemic plasma had no effect. He later repeated these studies in man and obtained similar results. The observa-

tions of Hahn have been confirmed in different animal species in various laboratories.

D. M. Graham and co-workers (*Circulation* **4,** *666* (*1951*)) have shown that heparin administered intravenously to rabbits and human beings causes a redistribution of the plasma beta-lipoproteins. They found a decrease in the concentration of lower density beta-lipoproteins (high S_f rates) and a concomitant increase in beta-lipoproteins with a higher density (low S_f rates). Since there was no change in total beta-lipoprotein concentration, this implied a shift of the beta-lipoproteins with higher S_f rates into those of successively lower S_f rates. Heparin administered to cholesterol-fed rabbits retarded the usual build-up of S_f 10 to 50 lipoproteins as well as the development of atherosclerosis. In human subjects, accompanying the redistribution of lipoproteins following heparin injection there was said to be a marked reduction in the symptoms of angina pectoris in 55 of 59 patients with histories of this disease.

The mechanism of the action whereby heparin causes clearing of lipemic plasma and redistribution of the lipoproteins has been brought under investigation by several laboratories in the last few years. N. G. Anderson and B. Fawcett (*Proc. Soc. Exp. Biol. Med.* **74,** *768* (*1950*)) found that heparin intravenously injected in human subjects caused the formation of a surface-active substance in the plasma. Anderson and Fawcett believed this active substance, which has been termed clearing factor, to be a heparin-phospholipid complex. Postheparin plasma (plasma obtained fifteen to thirty minutes after the administration of heparin) which contains this factor will clear lipemic plasma when the two are mixed *in vitro*.

C. B. Anfinsen, E. Boyle, and R. K. Brown (*Science* **115,** *583* (*1952*)) attempted to purify and clarify the *in vitro* system described by Anderson and Fawcett. They found that a tissue factor in addition to heparin was needed for the formation of clearing factor. The clearing factor so formed in the presence of an acceptor protein ("coprotein") may then cause the clearing of lipemic plasma and the redistribution of the lipoproteins. A report from this laboratory by Brown and D. L. Kauffman (*Fed. Proc.* **12,** *183* (*1953*)) described a soluble stable tissue factor prepared from lyophilized rat pylorus. Recently B. Shore, A. V. Nichols, and N. K. Freeman (*Proc. Soc. Exp. Biol. Med.* **83,** *216* (*1953*)) have observed that during the clearing reaction there is a "partial hydrolysis of the glyceride component of the lipoprotein with concomitant release of fatty acids."

Further information on the nature of the heparin-induced clearing reaction has been adduced by R. S. Gordon and co-workers (*Proc. Soc. Exp. Biol. Med.* **84,** *168* (*1953*)) working in the United States and by E. A. Nikkilä and E. Haahti (*Acta chem. Scandinav.* **8,** *363* (*1954*)) in Finland. Gordon *et al.* found that the albumin fractions of plasma were rich in acceptor protein (termed by them "coprotein"). They hypothesized that "coprotein" probably functioned in the lipemia clearing reaction by binding the fatty acids liberated by clearing factor. Nikkilä and Haahti (*loc. cit.*) prepared protein fractions from human serum by a continuous electrophoretic method and tested them for their ability to initiate *in vitro* clearing of a system containing purified clearing factor and an olive oil emulsion. They concluded, in agreement with Gordon *et al.*, that the acceptor protein was either serum albumin or a protein intimately associated with it. Nikkilä and Haahti concluded from further studies that the clearing factor might be a lipase activator, or, alternatively, that fat splitting might be secondary to the alteration of the physiochemical state of fats brought about by the heparin-induced clearing reaction. They further found that the substance extracted from duodenum by Brown and Kauffman (*loc. cit.*) was probably not a "tissue factor" at all but a lipase.

Although the mechanism of the heparin-induced lipemia clearing reaction has not been fully elucidated, it appears likely that

heparin in conjunction with a factor from plasma forms a complex (clearing factor) which has lipase or lipase-activating properties. A tissue factor may activate the formation of this clearing factor. The latter substance in the presence of plasma albumin ("coprotein," acceptor-protein) causes clearing of plasma lipemia, redistribution of lipoproteins, and liberation of fatty acids. The albumin probably functions by binding the liberated fatty acids.

The pertinence of these interesting studies to the problem of human atherosclerosis is by no means clear. The lactescence of plasma is caused largely by the very low density chylomicrons (S_f 40,000). The lipoprotein classes which have been implicated in the genesis of atherosclerosis are those of the S_f 0 to 400 classes which have only minimal light-scattering properties and which are not dramatically diminished by heparin treatment (H. L. Chandler, E. Y. Lawry, K. G. Potee, and G. V. Mann, *Circulation* **8,** *723 (1953)*). These studies of Gordon *et al.* and of Nikkilä and Haahti with heparin appear to have more promise in the light they may shed upon the physiologic mechanisms of fat metabolism which are presently only crudely understood.

NUTRITION AND ADULT BODY DIMENSIONS

In several studies it has been noted that individuals of foreign descent who come to live in the United States tend to exceed their countrymen in stature and some other body dimensions. The interpretation of these differences remains controversial, involving selective migration on the one hand and environmental influences, including diet, on the other hand. G. W. Lasker (*Human Biol.* **24,** *262 (1952)*) has undertaken a study designed to assess the relative importance of these two sets of factors by comparing individuals who left their country, at different ages and for various periods of time, with the dimensions of those who stayed home.

It was necessary, for the purposes of this study, to choose a community with a fairly high proportion of returned migrants and with environmental factors (dietary, climatic, sanitary) which differed from those experienced by the immigrants in the United States. The town of Paracho, in the west central Mexican state of Michoacan, corresponded to the specifications. A detailed dietary survey has not been made, but on inspection the diet appeared of good quality, ordinarily adequate in quantity. Absence of more detailed information about the diet is one of the weak points in the study, even though the reviewer realizes full well the difficulties involved in gathering such data.

The study shows that only those emigrants from a Mexican town who left home before the age of 27 years differed physically from those who remained in Mexico. The returned emigrants are significantly larger in many respects. Those who had left Mexico before the age of 17 showed larger increments in body dimensions than those who first went to the United States between the ages of 17 and 27. The young immigrants have also stayed longer in the United States. The general increase in body size seems to reflect environmental differences. A more adequate and abundant diet available to the still-growing emigrants in the United States is considered the probable crucial factor.

The relationships between food supply and body weight in Great Britain during the years 1943 to 1949 were examined by J. M. Harries and D. F. Hollingsworth (*Brit. Med. J.* **1,** *75 (1953)*). The data were collected for the Ministry of Food with the aim of providing an independent check on the adequacy of the national food supply. Data for two groups of adults (industrial workers in small plants and working-class

women) between 25 and 54 years of age indicate an average rise in body weight from 1943 to 1945 (about 2 pounds for men, 3 pounds for women), then a moderate decline of less than 1 pound, followed by a rise of 2 to 3 pounds, beginning in 1947. In all three phases the changes in body weight paralleled the trends in the energy value of the foods consumed, using the domestic food consumption of urban working-class households as the criterion of food supply. The caloric fluctuations were of the order of 120 to 140 calories per individual per day.

It is unfortunate that the average age of the samples in successive years was not given. While the caloric intake level in 1944 was the same as in 1949, there was an average weight increment of about 1½ pounds for men, and about twice as much for women. This would suggest that the weight variations associated with fluctuations in the diet were superimposed on a secular trend toward higher average weights. Do these changes reflect simply the aging process during the period of maturity?

While the weight increases are not open to a simple interpretation, the weight losses may be regarded—in the absence of changes in bodily activity—as a warning that the food supplies are inadequate. In Great Britain the weight was kept constant with the average daily intake of 2900 calories. A decrement below this level resulted in a publicly voiced dissatisfaction over the food supply, and adults lost weight. Increase of the caloric intake above 2900 calories reversed the downward trend.

MUSCLE GLYCOLYTIC ENZYMES IN MUSCULAR DYSTROPHY

Many types of progressive muscular dystrophy have been described, but generally cases fall into two main varieties: (1) those which occur in early childhood, predominantly in males, and which are usually considered to be inherited as a sex-linked recessive; and (2) those which appear in late childhood or adolescence and have gone under the name of the facioscapulohumeral or Landouzy-Déjerine type, and appear to be inherited as a Mendelian dominant with an equal sex distribution. The first type usually progresses relatively rapidly to early death before adult life is reached. The second variety is less severe and less rapidly progressive and involves the facial muscles and the pectoral girdle particularly, in contrast to the childhood type in which the pelvic muscles are usually first involved, followed shortly by affection of the trunk muscles.

Although it has been assumed by many workers in the field that some one or group of biochemical defects occurs in the muscles of these patients, none has been shown. The only biochemical abnormalities have been increased urinary creatinine and diminished creatine excretions (*Nutrition Reviews* **10,** *165 (1952)*). Of interest, therefore, are the striking and marked decreases in the muscle content of phosphorylase and aldolase in this disease reported by J.-C. Dreyfus, G. Schapira, and F. Schapira (*J. Clin. Invest.* **33,** *794 (1954)*).

Muscle biopsies, obtained under general anesthesia, were frozen in liquid nitrogen. The method of Cori and Cori was used to measure phosphorylase activity of muscle, and aldolase was determined both by the method described by Dounce, Beyer, and Barnett, and by that of Sibley and Lehninger. All determinations were referred to noncollagen nitrogen; that is, the quantity of collagen and elastin nitrogen was determined as that insoluble in alkali, the soluble nitrogen being that not obtained from collagen. The importance of this refinement in the study was shown by comparison of the content of collagen nitrogen in the biopsies from the 9 normal individuals

used as controls with that of 18 patients with progressive muscular dystrophy, the former showing a mean of 12.6 per cent collagen nitrogen and the latter 34.2. Almost no overlap was present between the two groups and many of the dystrophic subjects had between 40 and 50 per cent collagen nitrogen. In general, the more severe the disease the higher the collagen nitrogen, confirming the marked increase in fibrous tissue previously observed by histologic examination of the muscles from these subjects.

Both phosphorylase "a" activity (without the addition of adenylic acid) and phosphorylase "b" activity (the activity in the presence of adenylic acid) were determined. A marked decrease in both phosphorylases per gram of noncollagen protein was found in the patients as compared to the control subjects (a mean of 2890 units compared to 8590 units). With respect to phosphorylase "b" the same held true, there being a mean of 4640 units per gram of noncollagen protein in the patients as compared to 12,570 in the control subjects. One of the patients showed a muscle phosphorylase "a" activity as high as that of the control subjects and in one other the phosphorylase activity was exceedingly low. This patient, in whom both types of phosphorylase activity were very low, had the most severe disease as judged clinically. Aldolase was likewise strikingly decreased in the muscles from the patients, the mean being 6.6 units per gram of noncollagen protein for the patients compared to 20 units for the control subjects. The aldolase activity of the serum was higher in the patients than in the control subjects. The authors mention that the aldolase activity in the serum of patients with other neuromuscular disorders was normal, although the data are not presented.

In addition to phosphorylase and aldolase, the muscle iron was analyzed, presumably that which is "not included in chromoproteins, myoglobin, and the cytochromes." Expressed as milligrams of iron per 1000 g. of dry noncollagen protein, no significant difference was found between the control subjects and the patients with progressive muscular dystrophy.

The authors are properly conservative in their conclusions, pointing out merely that there is a decrease in phosphorylase and aldolase in the muscles of patients with progressive muscular dystrophy and not implying whether this decrease represents the fundamental biochemical lesion or is the result of some other deficiency. The study represents an interesting step forward in our knowledge of this disease.

NUTRITIONAL STATUS STUDIES

In order to maintain an index of the nutritional conditions among the people in this country, large-scale nutritional status surveys have been advocated. Only a small number of such studies have been carried out during the past ten years. One of these covering a variety of population groups in six northeastern states has now been completed and the results published as a series of Experiment Station bulletins. The primary purpose of the study was to evaluate the methods used and to determine what correlations existed between the dietary, biochemical and clinical findings.

Shortly after funds were made available for cooperative research projects among the Agricultural Experiment Stations, this large-scale nutritional status study was initiated in 1947. In Maine 367 male and 409 female junior high school students were examined. Approximately half of these came from a small city in the central part of the state; the remainder from nearby towns. Almost a third of the students from the towns came

from farm homes. In Massachusetts 79 pregnant women living in Amherst were studied. In New Jersey 606 male employees of four companies engaged in the manufacture of chemical and pharmaceutical products were studied. These men were over 20 years of age and included subjects with a wide range of income and educational background. In New York 362 boys and 312 girls, ranging in age from under 13 to a little over 16, were studied. These students attended four schools in the central and southern part of the state. Most of these were from cities. In Rhode Island the subjects were 64 boys and 224 girls, ranging in age from 13 to 20. They represented both rural and urban areas. In West Virginia 210 boys and 125 girls, ranging in age from 16 to a little over 20, were examined; they were students at the University.

Before the study started, the investigators agreed upon most of the technics that were to be used. These included physical examinations, patterned after the physical signs suggested as being associated with nutritional deficiencies by H. R. Sandstead and R. K. Anderson (*Pub. Health Reports* **62,** *1073 (1947)*); biochemical analyses of the blood according to the microchemical technics of Bessey and Lowry (O. A. Bessey, *p. 287 in Vol. 1,* "Vitamin Methods," edited by P. György, *Academic Press, Inc., New York (1950)*); and dietary histories. The technics are described in some detail in *Cornell University Agr. Exp. Station Memoir 307, March 1951.* This report is especially valuable since it indicates the pitfalls that may occur in some of the microchemical technics. Suggestions are made as to how to overcome these difficulties.

In each state physical examinations were made by local physicians. An attempt was made to standardize the forms used for the clinical examination. However, the variation in problems and the types of subjects in the different states precluded exact standardization. In a few of the states studies were made of the variation in the interphysician recognition of physical signs. This was done by having a large group of subjects randomly sent to 2 or more clinicians. On this basis it was assumed that the incidence of clinical signs seen by each examiner would be equal; any differences under these circumstances were ascribed to variations in reporting by the physicians.

In New Jersey the physicians agreed very well on the incidence of deficiency signs. The physicians in Maine and New York did not agree quite so well. In the latter cases the samples may not have been so randomly distributed as in New Jersey since one physician examined the children in one school, while another physician examined those in other schools. The greatest divergence of results occurred in all cases in the reports on the vascularity of the bulbar conjunctiva (blood supply of the mucous membranes covering the eyeball), followed by thickening of the bulbar conjunctiva, inflammation of the palpebral conjunctiva (mucous membranes lining the eyelids), and stomatitis (inflammation of the mucous membrane of the mouth). In New Jersey the 5 physicians reported the same incidence of dermatitis, xerosis (dryness of the skin), blepharitis (inflammation of the eyelids), nasolabial seborrhea (excessive secretion of oil around the nose and lips), swelling of the tongue, atrophy of the skin, and neurologic abnormalities; they also rated the general appearance of the subjects in the same manner. It should be noted that these studies differ from others in the literature, such as that of W. B. Bean (*J. Applied Physiol.* **1,** *458 (1948)*), where the same subjects were seen by a number of physicians. Under those circumstances there was considerable variation in the reports of different clinicians.

In each state approximately a third of the subjects were within 5 per cent of their "normal" weight as judged by standard

height-weight tables. Approximately the same percentage of subjects was underweight; and there was a tendency for the percentage of underweight subjects to increase with age. There was, however, no correlation of overweight (10 per cent or more above "desirable" weight) with age. Approximately 23 per cent of the males and 20 per cent of the females were in this category.

Each state had a small percentage of subjects showing physical signs that might be related to nutritional deficiencies. For most of the signs, the highest incidence occurred among the school children in Maine and the pregnant women in Massachusetts. A very high percentage of all subjects other than those in Maine were rated as having a good general appearance.

The third report in this series, on dietary methodology studies (*Massachusetts Agr. Exp. Station Bulletin No. 469, August 1952*), provides an exhaustive review of the literature. On the basis of the earlier work, the nutritionists concluded that to secure a valid dietary intake for an individual, daily dietary information covering a week was necessary, and that one-day dietary studies may provide information on the food habits of population groups. Previous studies had also indicated that there might be a variety of errors in the different methods used in dietary surveys.

All of the cooperating groups collected both a dietary history modeled on that of B. S. Burke (*J. Am. Dietet. Assn.* **23,** *1041 (1947)*) and the seven-day dietary record (except in Maine, where four-day records were taken). These records were secured on only a small fraction of the entire group. The daily nutrient intake for each subject was calculated on the basis of both methods. A comparison of the two methods showed that the one-day dietary history did not give the same estimate of intake for the same individual as the seven-day record. The differences between the two methods were least among the college students. These were largely nursing, premedical, or home economics students. The experience and interest of these students in nutrition probably accounted for the close agreement between their two sets of records. For the school children the differences in nutrient intake, as judged by the two technics, ranged on an average for the group from 20 to 60 per cent for the ten nutrients studied. The results for the pregnant women and industrial workers fell in between the college students and the children. For all the nutrients studied, the closest agreement between the two methods occurred in the case of calories, iron and thiamine.

In order to determine how accurately a seven-day dietary record reflected an individual's true dietary habit, a special dietary study was carried out with 16 women and 2 men. The subjects kept a record of estimated food intakes for twenty-eight consecutive days from mid-October to mid-November. Calculation of nutrient intake on a daily basis showed that for seven of the ten nutrients studied approximately half of the individuals had weekly averages that varied within ±10 per cent of their twenty-eight-day average. These nutrients were calories, protein, phosphorus, iron, thiamine, riboflavin and niacin. For calories, protein and iron all of the individuals had weekly averages that were within ±20 per cent of their twenty-eight-day averages. The vitamin A and ascorbic acid intakes showed the greatest weekly variation. Three fourths of the subjects had weekly averages of vitamin A intakes that deviated more than ±20 per cent from their twenty-eight-day averages. More than 40 per cent of the subjects showed deviations in their weekly ascorbic acid intake of ±20 per cent from their twenty-eight-day average. The weekly calcium intakes for about one third of the individuals differed by more than ±20 per cent from their twenty-eight-day average.

In another study the nutrient intake of a small group of 22 eighth grade pupils was determined by three different methods. A

nutritionist in an interview secured a record of the food eaten by the child in the preceding week. At another interview, the mother was questioned as to the child's food intake for that week. Neither the child nor the mother knew that such a diet history was going to be taken, nor did they know that the other member of the family was to be questioned. After that, a seven-day record of food intake was kept by each child. The boys' estimate of their one-day food intake was higher than was evident from their mothers' reports; however, their seven-day diet records showed lower daily nutrient intakes than either of the other two methods. The girls' recollection of their food intake agreed fairly closely with their mothers' estimate, while the girls' seven-day diet records gave lower values.

Another special study was made of the subjects' ability to estimate food portions. From this, it was concluded that errors in estimating portion sizes are probably the largest source of error in diet record keeping. There was considerable variation in the ability of different groups to estimate the size of food portions; those with training in foods are most accurate in this respect. Foods that can be served in easily measured portions, such as bread, rolls, cookies, eggs, glasses of milk, cups of soup, etc., can be estimated most accurately. Foods such as puddings, sauces, gravies and fruits were least accurately reported. Between these two extremes are meats, vegetables, salads and casseroles.

The above report is of importance to anyone concerned with dietary surveys. It covers all phases of the work in an exhaustive manner. The report would be considerably more useful if it were presented in a cohesive manner—it consists of a series of papers written by different people who did not integrate their report with those that preceded or followed it. In some cases, complex statistics are used in the presentation of the results.

The dietary findings are presented in *Rhode Island Agr. Exp. Station Bulletin 319, June 1952.* The average nutrient intake is given for the different age and geographic groups. The results demonstrate that the most prevalent deficiencies in the diets of children, as shown by comparison with the Recommended Dietary Allowances of the Food and Nutrition Board (*National Research Council Reprint and Circular Series No. 129, Washington (1948)*), were ascorbic acid, vitamin A, calcium and riboflavin. For the other nutrients, only a small percentage of the subjects consumed two-thirds or less of the recommended dietary allowances. More adult males than females met the recommended allowances. This was especially true for iron, protein and niacin.

The results of the biochemical analyses of the blood are described in the *Maine Agr. Exp. Station Bulletin 516, May 1953.* In order to minimize the day-to-day variation in the analytic procedures, each laboratory analyzed a standard serum sample along with their survey samples. This standard serum sample was taken from one individual, usually on the same day survey samples were taken. A portion of this blood was run each time analyses were carried out. Additional precautions were taken by sending referee serum samples to each of the cooperating laboratories. The variations among the cooperating stations in the values reported for ascorbic acid and carotene were approximately equal to the day-to-day variations of these constituents in the blood of the individual subjects. It is implied that the variability in the analytic results for vitamin A was much greater. Unfortunately, no results are given for these interlaboratory studies.

Distribution charts are given for the hemoglobin contents of the blood from the different groups studied. Low mean hemoglobin values were found frequently among the 16 to 20 year old girls in Maine and Rhode Island and the pregnant women in Massachusetts. The ascorbic acid levels in the serum decreased with increasing age for

both boys and girls. The younger children showed no sex difference in this respect. After age 13 to 15, the serum ascorbic acid values were significantly lower for the boys than for the girls. The mean values for the teen-age boys and girls in Maine were lower than the values for the similar age groups in the other states. The industrial male workers in New Jersey had an average of 0.77 mg. per 100 ml. of serum. This was significantly higher than that for college students studied in West Virginia. There was a large group, especially among those who were 13 years of age or older, with serum ascorbic acid values below 0.4 mg. per cent. The serum vitamin A values for the teen-age girls in Maine were lower than those for the same group in New York and Rhode Island. Although there was some variation in the serum values for the other groups, the only significant finding was the large number of teen-agers who had values below 20 micrograms of vitamin A per 100 ml. of serum. A similar situation existed among the teen-agers in the case of carotene.

The correlations between the different items studied in the surveys are presented in the *West Virginia Agr. Exp. Station Bulletin 361T, June 1953.* Significant correlations are observed in two or more of the geographic and age groups for hemoglobin with dietary protein, hemoglobin with dietary iron, blood vitamin A with blood carotene, and blood ascorbic acid with dietary ascorbic acid. There was closer agreement between the analytic results on the blood samples and the occurrence of physical signs associated with nutritional deficiencies than there was between these signs and the individual's reported dietary intake. Should this relationship be maintained in other surveys, it would indicate that more attention should be given to the microchemical blood methods as valuable tools in nutrition surveys.

These reports are of considerable importance in showing that extensive and elaborate planning must go into any large-scale nutritional survey. An undertaking of this magnitude is a very costly one. For this reason each survey should be planned as carefully as possible to insure that the desired goals are kept clearly in mind. If the above survey was aimed at an evaluation of the general nutritional health of the people in the northeastern part of the United States, more attention should have been given to the selection of the subjects in the different areas. Although the report frequently refers to the random samples used, it is obvious that if randomization was used, it was done so within very restricted groups. For instance, among the college students only premedical, nursing and home economics students were chosen. These subjects were obviously more interested in their dietary intakes than were other subjects. It is also possible that many individuals would refuse to cooperate in a project requiring as much time and effort on the part of the subject as this one did. For this reason, the report on the variations in nutritional status in the different age, sex and geographic groups should be considered with the above limitations in mind. The reports do, however, present a rather exhaustive discussion of the technics and procedures to be followed in nutrition surveys and will be of value to all workers in the field of human nutrition.

HYPOPROTEINEMIA AND ACTIVITY OF SERUM AMYLASE AND LIPASE

Since enzymes are proteins, it is reasonable to assume that conditions which alter the protein content of a tissue would change the enzymes produced or contained in that tissue. By the procedure of limiting the protein intake of animals it has been demonstrated that the activity of a variety of enzymes in the liver is reduced. Among the

enzymes so studied in liver have been catalase, xanthine oxidase, alkaline phosphatase, arginase, cathepsin, succinoxidase and fatty acid oxidase (*Nutrition Reviews* **9,** *103 (1951)*; **11,** *23, 57 (1953)*). Investigations which would relate serum protein concentration to enzyme activity have not been so numerous nor the results so conclusive.

A recently published report is concerned with the activity in serum of two enzymes, amylase and lipase, in patients suffering from malnutrition and nutritional edema. This study is reported by K. L. Mukherjee and G. Werner of the School of Tropical Medicine in Calcutta, India (*J. Lab. Clin. Med.* **43,** *727 (1954)*). Fifteen patients were included in the group studied. All were hospitalized and exhibited signs of nutritional edema. No patient who suffered from other specific diseases which might have contributed to the occurrence of these manifestations was included in the group under study. The authors do not state whether the diets of these patients were examined for evidences of inadequate intake of protein.

This, then, was primarily a laboratory investigation of concentrations of serum total protein and albumin and of the activity of serum amylase and lipase. Methods which have been used widely in other laboratories were adapted for this study.

There was a range in concentration of serum albumin from 1.1 to 4.5 g. per cent. The activity of the enzyme amylase in serum varied from a low of 33 units to a high value of 261 units. The mean activity of amylase as determined in the serum of a group of normal subjects was 200 ± 31 units. There was a high degree of correlation between amylase activity and albumin concentration in the patients with nutritional edema. However, linear regression demonstrated that this relationship was only of significance when albumin levels were 2.5 g. per cent or less. The authors express the opinion, therefore, that amylase activity is independent of serum albumin when concentrations are greater than 2.5 g. per cent, but varies directly with serum albumin when concentrations of this protein in the serum are at levels less than 2.5 g. per cent. In this low range there was a decrease of approximately 40 units of amylase activity for each decrease of 0.1 g. per cent of albumin. In contrast to serum albumin, the concentration of total serum protein bore no significant relationship to amylase activity. The range of values for total serum protein in this group of 15 patients was from 2.9 to 6.8 g. per cent.

Lipase activity was found not to vary with concentrations of either serum albumin or total serum protein in the range found in these patients. Mean values of serum lipase were similar in this group with nutritional edema and in a control group of normal subjects.

The authors point out that changes in circulating plasma volume which are frequently associated with nutritional edema could not account for the decrease in amylase activity with decreasing concentrations of serum albumin below 2.5 g. per cent. They conclude that albumin bears an important relationship to the protein component or apoenzyme of amylase. As further evidence they state that with supplementation of the diets of their patients amylase activity increased only after serum albumin had increased also. It is of interest that other investigators have offered evidence that the cholinesterase activity of human serum varies directly with the concentration of serum albumin (M. Faber, *Acta med. Scandinav.* **114,** *72 (1943)*; H. G. Kunkel and S. M. Ward, *J. Exp. Med.* **86,** *325 (1947)*).

The failure of Mukherjee and Werner (*loc. cit.*) to demonstrate any change in serum lipase activity in nutritional edema is in contrast to the finding of decreased serum lipase in children with kwashiorkor (H. C. Trowell, J. N. P. Davies, and R. F. A. Dean, *Brit. Med. J.* **2,** *798 (1952)*;

Nutrition Reviews **12,** *5 (1954)*). The explanation is offered that nutritional edema and kwashiorkor may not be similar or even related nutritional deficiency disorders. However, the bulk of the currently available information indicates that both are contributed to by, if not the direct result of, protein deficiency.

COPPER METABOLISM AND AMINO ACID EXCRETION IN WILSON'S DISEASE

Certain of the abnormalities of copper metabolism in various disease states including Wilson's disease and the aminoaciduria so often found in this latter condition have been discussed several times (*Nutrition Reviews* **7,** *115, 255 (1949)*; **8,** *252 (1950)*; **11,** *296 (1953)*; **12,** *198 (1954)*). Two further investigations have added to our knowledge (A. G. Bearn and H. G. Kunkel, *J. Clin. Invest.* **33,** *400 (1954)*; W. H. Stein, Bearn, and S. Moore, *Ibid.* **33,** *410 (1954)*. Seventeen patients with Wilson's disease were compared with 23 patients with cirrhosis of the liver and 12 normal individuals. Twelve of the patients with cirrhosis had "nutritional Laennec's cirrhosis," 4 had biliary cirrhosis, and 7 had liver disease of unknown etiology. The previously reported finding of a reduced serum copper concentration, an increased urine copper excretion, and a reduced serum copper-protein complex (ceruloplasmin) were confirmed in these studies. The aminoaciduria usually but not always present in Wilson's disease was found in 16 of the 17 patients. Likewise confirmed was the parallelism between the serum copper concentration and oxidase activity, presumably indicating that the ceruloplasmin is an oxidase.

The distribution of copper among the various plasma proteins was studied electrophoretically in a starch-supporting medium. It was found difficult to exclude contaminating copper so that purified human albumin was added to the starch block in front of the advancing column of the serum to be analyzed. In this way copper not bound to ceruloplasmin became bound to the albumin and advanced with it. In normal individuals and patients with cirrhosis two peaks of copper were found, the first combining with the added albumin and the second residing in the alpha-2 globulin, presumably the ceruloplasmin. The patients with Wilson's disease showed the first curve, but not the second, indicating the marked reduction in ceruloplasmin as previously reported by I. H. Scheinberg and D. Gitlin (*Science* **116,** *484 (1952)*), using different technics.

The urinary excretion of alpha amino nitrogen and copper were studied in relation to changes in the dietary protein intake in 2 of the patients, and a striking parallelism was found. In the first patient an increase in dietary protein from a normal intake to 200 g. a day increased the excretion of alpha amino nitrogen from 200 to 1000 mg. daily and the copper from approximately 1000 to 1400 micrograms daily. In contrast, the reduction in dietary protein from 200 g. to a very low level in a second patient caused a prompt drop in the urinary copper excretion (from 1200 to 600 micrograms daily) and in alpha amino nitrogen (from 600 to 800 to approximately 200 mg. daily). In both these studies the reverse change in dietary protein led to inverse changes and return of both the urine copper and alpha amino nitrogen excretion to former levels.

The administration of cortisone also led to both an increased alpha amino nitrogen and copper excretion. BAL increased urinary copper excretion as has been reported previously. "Versene" intravenously administered increased urinary copper excretion, but neither "Versene" nor BAL affected the urinary alpha amino nitrogen excretion.

The individual amino acids in the plasma and urine of patients with Wilson's disease were measured by chromatography, using columns of Dowex 50. The plasma amino acid pattern was perfectly normal, confirming the previously found normal total alpha amino nitrogen in patients with Wilson's disease. In the urine, however, not only was there an increase in amino acids, but the individual amino acids in the urine showed an abnormal pattern, threonine and cystine being excreted in amounts the highest above normal, and others less so. Proline and citrulline, not found in normal urine, were present.

These data on the urinary excretion of copper, alpha amino nitrogen and individual amino acids suggest that the defect in the kidney is not simply decreased tubular reabsorption. This has also been postulated by others (*Nutrition Reviews* **8,** *252* (*1950*)).

As a hypothesis to explain these and the other phenomena in Wilson's disease, the authors submit the following: increased absorption of copper leads to its accumulation in the tissues and appearance in the urine. Cirrhosis develops if copper accumulation in the liver is excessive, and renal tubular damage follows copper damage to the kidneys, the latter leading to increased urinary excretion of amino acids, peptides, and, as the authors and others have found occasionally, glucose as well.

BODY WEIGHT AND ELECTROCARDIOGRAPHIC PATTERNS

Contractions of the heart are associated with weak electrical currents. The electrocardiogram, a graphic record of the amplified currents, is a valuable diagnostic aid in heart disease as well as a physiologic indicator of the conduction of nervous impulses within the heart and the activity of the heart muscle. The normal electrocardiogram (ECG) shows upward and downward deflections which are due to the contraction of the auricles (P wave) and the ventricles (deflections Q, R, S, and T). The direction and the size of the deflections, and the duration of several segments of the heart cycle represent the basic ECG data.

The variety of electrocardiographic manifestations, whether in health or associated with clinical evidences of heart disease, has made electrocardiography a medical specialty. Much of the literature is accessible only to individuals initiated into the terminology and symbolic representation of the leads. Nevertheless, some of the information is relevant to the science of nutrition.

The electrocardiograms of 32 young men in starvation and subsequent rehabilitation were examined quantitatively by E. Simonson, A. Henschel, and A. Keys (*Am. Heart J.* **35,** *584* (*1948*)). During starvation, consistent changes occurred in a large number of electrocardiographic measurements and the electrocardiograms would have been interpreted as abnormal in many subjects. There was a pronounced slowing of the heart rate. The amplitudes of all deflections decreased during starvation and recovered slowly in the course of nutritional rehabilitation.

The changes in electrocardiographic patterns associated with changes in the body weight of patients were examined by A. H. Kadish (*Am. Practitioner* **4,** *513* (*1953*)). In this paper evidence was presented of alterations in the electrocardiographic tracings associated with upward and downward fluctuations of body weight in patients with normal blood pressure. Kadish studied 4 patients in whom increase of body weight was associated with the appearance of electrocardiographic abnormalities while the loss of weight was followed by a return to a more normal ECG.

E. Simonson and A. Keys (*Circulation* **6,** *749* (*1952*)) examined a large number of

electrocardiographic values in clinically normal young and middle-aged men in reference to interindividual *differences* in relative body weight. In general, the influence of the relative body weight on amplitude of deflections was more prominent in the older than in the younger men. With increasing body weight, as might have been anticipated, there was a pronounced tendency toward a more horizontal position of the heart, determined from the electrocardiographic pattern. As a practical matter, it appears that a weight correction is desirable for a more precise definition of normal electrocardiographic standards and the evaluation of a departure from normality. This is particularly relevant for the consideration of ECG records on the borderline between health and disease.

At the same time, the data on differences in the ECG patterns with increasing relative body weight can be considered from the point of view of medical interpretation. This must be done with caution, as *all* of the subjects—light and heavy—had been considered clinically normal. Nevertheless, most of the measurements tended with increasing body weight toward those characteristic of arteriosclerotic changes. The differences are similar to those of age trends obtained comparing healthy young and middle-aged men. The age trends were, in general, in the direction of electrocardiographic abnormality and could be considered as indications of progressive degenerative changes of the heart muscle. It should be noted that the effect of overweight on the electrocardiographic pattern was more pronounced in the older men than in the younger group.

The relationship between underweight-overweight, as a fundamental "constitutional" variable, and 2 spatial ECG vectors (QRS and T) was investigated by E. Simonson and A. Keys (*Circulation* **9,** *105 (1954)*). Clinically, the highly significant difference in the angle between the 2 vectors observed in underweight (mean value 48.5 degrees) and overweight persons (60.4 degrees) is of particular interest. This effect, while within "normal limits," is in the direction of inadequate blood supply to the left ventricle.

Several studies in which *changes* in body weight were associated with alterations of the electrocardiogram and in which *differences* in the electrical activity of the heart were established in groups of individuals differing in relative body weight have been reviewed. Overweight was found to be associated with electrocardiographic features suggestive of a tendency to myocardial degeneration. Although the groups studied were screened for normality and absence of symptoms, and did not include extremes of emaciation or obesity, the electrocardiographic trends in these "normal" men are compatible with the higher incidence of degenerative heart disease in obese subjects.

FOOD FADS AND FANCIES

In a talk presented before the 125th Annual Meeting of the Division of Agriculture and Food Chemistry of the American Chemical Society, H. L. Sipple and C. G. King (*J. Agr. Food Chem.* **2,** *352 (1954)*) have described a health problem arising because of the flourishing activities of food faddists. These scientists point out that our food supply is the best that we have ever had, and that there is a high standard of protection for our food supplies. However, they report that the dietary habits of approximately 10 million of the United States population is being influenced by nutrition quacks. The health of a significant number of these individuals is being endangered both by the unsound dietary recommendations of these faddists and by frequent delays in seeking necessary medical treatment until it is too late to be of value.

It has been estimated that about one-half billion dollars per year is being spent for "health foods," "health aids" and "diet supplements," on behalf of products for which no real need has been demonstrated or which are unnecessary for the purchaser. This does not refer to and should not be confused with legitimate, beneficial practices based on sound advances in the science of nutrition.

Sipple and King point out that the old-time medicine man who was actually yesterday's nutrition quack sold his cure-all, youth-restoring patent medicines to any small groups which he could attract on a street corner, in a vacant lot, or at picnics and fairs. However, with improvements in communication, an informed public soon became conscious of the complete ineffectiveness of his products. Instead of disappearing with the changing times and conditions, the medicine man became "a food expert," dealing in health foods and diet supplements instead of patent medicines and using every form of modern advertising and means of communication. Sipple and King state, "Whether the 'expert' is a lecturer-author, pseudoscientist crusader, writer of sensational articles and books, or a high pressure salesman appearing on radio and television, fundamentally the food faddist is a fluent speaker or writer. He is willing to make unrestrained and fantastic claims as to the value of his products or theories, disagreeing with established information and condemning generally recognized and authoritative scientific organizations, institutions and regulatory agencies and he always has something to sell." This often involves condemnation for a variety of common foods including pasteurized milk, fruits and vegetables produced with the aid of commercial fertilizers and cereal products described as having lost their important nutrients by reason of the mode of preparation. The faddish approach often takes advantage of widespread interest in such a problem as obesity, with the food faddist being keenly alert to the golden opportunity to exploit the fear of obesity and its effects. The promotion of reducing aids and diets of a variety of kinds has become one of the most profitable and active operations of the nutrition quack. All too commonly the promises are based on a way to reduce without dieting, obviously playing upon the wishful thinking that weight reduction can be achieved without a reduction in the caloric value of the food eaten below the calories expended.

These authors state that effective dealing with nutrition quackery is largely a continuous educational problem which requires focusing attention on both elementary and adult education. They urge instruction in the principles of good nutrition as a regular feature throughout elementary education beginning in kindergarten and integrated into existing related courses. They believe that a good beginning toward dissemination of sound nutritional information has been made by the educational programs of numerous food companies. In addition a coordinated program to augment the work of individual companies, educational agencies and health organizations is needed not only to expose and offset food faddism by replacing fantasy with fact, but also to meet the all-important continuing need for a practical guide to good nutrition in everyday life. It is their belief that it would be difficult to make a greater contribution to public health and to a more intelligent national economy.

The real concern of scientists about food faddism is further indicated by the symposium conducted at the spring meeting of the Federation of American Societies for Experimental Biology at Atlantic City, April 1954. On this occasion a half-day symposium was conducted on the subject under the leadership of L. A. Maynard, symposium chairman, C. G. King, E. Nelson, W. H. Sebrell, and A. Beeuwkes.

Obviously the need for sound educational

programs on the various phases of nutrition is very real. The highly successful dissemination of nutritional knowledge in the past three decades should encourage everyone in the nutrition field to believe in the future potentialities for further education of our fellow Americans. Each qualified individual in the various nutritional areas should take definite responsibilities to participate in such educational programs through whatever medium is possible in his or her own community.

JAPANESE INSTITUTE OF NUTRITION

The 1953 Annual Report of the National Institute of Nutrition in Tokyo, Japan, should prove useful since its work is little known in this country. It is unusual in that it contains many tables of the original data and thus allows some evaluation of the work even though the original reports are not available. This is a practice which might be adopted with benefit by other institutions. In a few places the translation is not clear and leaves the reader in doubt as to the findings and conclusion.

Several reports are related to basal metabolism and specific dynamic action (SDA). The specific dynamic action (increased calorie expenditure over the basal rate) was measured for both high carbohydrate and high protein diets. In the first, 13 per cent of the calories were derived from protein and 12 per cent from fat, while in the second the values were 40 and 15 per cent respectively. Meals supplying 600, 800, 1000 and 1200 calories were studied. The heat production does not fall to basal levels until approximately twelve hours after feeding. On the high carbohydrate diet the SDA amounted to 7.1, 6.3, 6.0 and 6.2 per cent of the calories supplied by the meals at the four calorie levels. Corresponding values for the high protein diet were 20.3, 16.2, 13.8 and 13.2 per cent of the calories ingested. On the high carbohydrate diet the SDA was roughly proportional to the calories fed at any time after feeding. On the other hand, the excess heat production during the first six hours after the high protein diets were given was essentially constant regardless of the number of calories fed, and then fell off more rapidly at the lower levels of caloric intake. It is concluded that the kind and number of calories must be considered in the calculation of SDA.

In the next report the two diets given above and a high fat diet, 40 per cent fat, 13 per cent protein, were included in a study of whether or not the calories consumed by specific dynamic action could be utilized for work. The SDA for the three diets are given as 8.0 per cent, 14.5 per cent and 8.6 per cent for the high carbohydrate, high protein and high fat diets respectively. Total number of calories given are not reported. The subjects walked at a moderate rate for an hour after the meal. The conclusion is reached that the total heat production is the sum of the SDA and the energy due to muscular work, that is, that the calories of SDA are not available for work, and that this is true for all three diets.

Several papers are concerned with calcium utilization and calcium metabolism in rats and man. It is stated that one of the diets fed to the rats was made to have a Ca:P:Mg ratio similar to the Japanese diet which is 1:6:1.5. Although the controls do not appear to be adequate, the authors concluded that when a diet containing 0.11 per cent of calcium was fed the high magnesium given did not appear to interfere with calcium utilization. This was based upon bone ash determinations. However, the control diet contained more calcium, 0.33 per cent, and 0.6 per cent phosphorus, and the animals on this diet grew better than those receiving the high magnesium diet. When the cal-

cium was raised to 0.266 per cent and the Ca:P:Mg ratio was maintained as above the animals grew poorly, the bone ash was essentially normal, but the animals developed hypertrophied kidneys, necrosis of the tubular epithelium and urinary calculi.

Calcium balance studies are reported upon 5 adult men. When they were fed a diet supplying approximately 500 mg. of calcium per day, 4 of the 5 were in negative balance during the first period of four days. All 4 improved markedly during the second period of five days on the same diet. It appears that about 500 mg. per day or somewhat less would maintain balance in these subjects. When the calcium intake was raised to 700 mg. per day by the addition of small fish the balance became positive and an 18 to 35 per cent utilization of the calcium from this source was calculated. This is in the same range as most dietary sources of calcium.

Several papers are concerned with the effects of oxalic acid on calcium utilization. The authors conclude that there is a seasonal effect, the interference with calcium metabolism being greater in the summer and winter, and that high protein diets are partially protective against oxalate effects. Since the studies are based upon rates of growth, protein efficiency and bone ash determinations, and the amount of protein causes large differences in the first two measures as well as food intake, there may be some doubt as to the comparisons made.

Among the several other papers is one concerned with the food intake of housewives from low-income families. Some of the average intakes given are 72 g. of protein, 2225 calories, 21.7 g. of fat, 3200 units of vitamin A, 1.5 mg. of thiamine, 0.68 mg. of riboflavin, 86 mg. of ascorbic acid, and 0.3 g. of calcium per day. Other papers along these lines include the determination of the expenditures for food at different income levels and the food preferences of tuberculous patients.

NUTRITION OF THE CHINCHILLA

The chinchilla is a South American rodent that was practically unknown in North America until 1923. In recent years the population of chinchillas in this country has increased rapidly and it is now estimated to be over 100,000 in the United States. Along with the rapid growth of the population have come demands for accurate nutritional information for this species. Data regarding the ascorbic acid and thiamine requirements of the chinchilla were published in 1952 by K. W. King and F. S. Orcutt (*see Nutrition Reviews* **11,** *80 (1953)*). They considered that their results were tentative due to the limited number of animals available for study and the lack of uniformity in performance of the test animals.

Recent additional data regarding the dietary requirements of the chinchilla have been presented by G. P. Larrivee and C. A. Elvehjem of the University of Wisconsin (*J. Nutrition* **52,** *427 (1954)*). The diet used by these workers was patterned after a synthetic diet developed in their laboratory for guinea pigs. They point out that anatomically the chinchilla and the guinea pig are similar in that they possess an unusually large functioning cecum. Such an observation was likewise utilized by King and Orcutt; consequently, the diet developed by Larrivee and Elvehjem was nearly the same as that reported in the earlier work. The percentage composition of the diet was as follows: sucrose, 37; casein, vitamin-free, 30; cottonseed oil, 4; salts, 4.0; vitamin mix, 2.0; potassium acetate, 2.5; magnesium oxide, 0.5; and gum arabic or cellulose, 20. The vitamin supplement contained the following (milligrams per 100 g. of ration): thiamine, 1.0; riboflavin, 1.4; pyridoxine, 1.0; biotin, 0.04; folacin, 0.3; menadione, 0.2; calcium pantothenate, 3.0; niacin, 10; para-amino-

benzoic acid, 10; inositol, 200; choline, 300; alpha-tocopherol acetate, 12; beta-carotene, 1.2; and calciferol, 0.008.

The experimental diet contained all of the known vitamins except ascorbic acid and vitamin B_{12}. Since the basal diet appeared to support growth equal to that obtained on conventional rations of rabbit or chinchilla pellets, ascorbic acid did not appear to be essential; this conclusion was also indicated from the earlier studies of King and Orcutt (*loc. cit.*). The Wisconsin workers tested dietary variations by omitting the potassium acetate and magnesium oxide supplements. This diet change did not lessen the growth rate over a short period.

Perhaps the most significant observation that was apparent from the Wisconsin studies was the superiority of cellulose as roughage when compared with gum arabic. Animals fed the diet containing gum arabic as roughage developed severe constipation and eliminated sharply reduced numbers of well-formed fecal pellets. Dosages of milk of magnesia and epsom salts elicited no response, but an immediate improvement was consistently observed when the gum arabic was replaced by cellulose as the dietary roughage.

Although the experimental objectives included determination of vitamin, protein, fat, carbohydrate and mineral requirements, most of these objectives must await further study. Pursuit of these objectives was interrupted by the appearance among the experimental animals of an epidemic bacterial enteritis. The data on dietary changes in minerals and roughages that were reported were obtained on a limited number of the original 67 chinchillas that were available for these studies.

Before concise nutritional data can be accumulated for the chinchilla, it is apparent that there is much still to be learned regarding disease problems and management under experimental conditions. The extent to which progress can be made will depend largely upon the extent to which animals are made available for experimental study. From the present limited data, however, it seems likely that synthetic diets that have been developed for guinea pigs should prove satisfactory for investigating the nutritional requirements of the chinchilla.

FERTILIZERS AND FOOD COMPOSITION

The important part that fertilizers play in agricultural crop production has become increasingly evident. In addition to the greater crop yields, data are becoming available which indicate a relationship between the use of fertilizers and the mineral composition of the plants grown in the fertilized soil. This offers potentialities for the improvement of plant composition insofar as the nutritive value for man and animals is concerned.

In a recent study by P. P. Chichilo, W. H. Armiger, A. W. Specht, and C. W. Whittaker (*J. Agr. Food Chem.* **2,** *458 (1954)*) blast furnace slag and agricultural limestone have been compared as sources of plant nutrients. On analysis, it was observed that the calcium content of the limestone was 55.6 per cent while that of the blast furnace slag was 33.6 per cent. Whereas the limestone contained relatively small amounts of aluminum, magnesium, manganese, iron, boron, copper and sulfur, the blast furnace slag contained appreciably higher amounts of these materials. The only plant tested in this particular study was sweet clover. Two different soils were used in the comparisons: one a Norfolk sandy loam and the other a Fallsington heavy loam.

On the heavy loam soil, the use of the furnace slag produced crops containing two to four times as much manganese, somewhat less calcium, and frequently more copper. On both types of soils, the use of furnace

slag produced crops containing up to two and one-half times as much magnesium and significantly more boron. Aluminum, iron, sodium, phosphorus and potassium contents were relatively unaffected in these trials. The average rate of emergence of the seedlings, nine days after seeding, was 50 and 63 per cent respectively on the unlimed and limed Norfolk soil; and 30 and 43 per cent on the Fallsington soil. The increased emergence after liming represented a significant improvement, but no significant difference was observed between the effect of the two liming materials used. On the light Norfolk loam, slag and limestone were equally effective in raising the pH, but the latter was found to be appreciably more effective on the Fallsington heavy loam. As an over-all effect, treatment with limestone produced higher yields of sweet clover on the Fallsington soil than treatment with slag. On the Norfolk soil the two materials were approximately equally effective with respect to the yield. This may be a reflection of the lesser alteration of the pH of the soil in the Fallsington type or it may be a reflection of the lower amount of calcium supplied by the slag. In this regard it is unfortunate that another treatment was not conducted throughout this study in which sufficient slag was added to supply an amount of calcium equivalent to that supplied by the limestone.

These studies are of interest for two reasons. First, it is important to note that the absorption of other materials than calcium was augmented by the use of furnace slag, suggesting that these materials were present in available form. Secondly, these increases in mineral components may have nutritive significance when these plant substances are used by animals. In addition, these studies indicate the potentialities for the use of a material as fertilizer which to a large extent in the past has been a waste product the disposal of which has been difficult.

Soil-conditioners also are beginning to play an important role in the maintenance of the quality of agricultural soils. These materials are designed to function as synthetic replacements for the natural polysaccharides and polyuronides derived from humus. One of the soil-conditioners has been found to influence the composition of the plants grown on soils into which it was incorporated (W. H. MacIntire, S. H. Winterberg, A. J. Sterges, and L. B. Clements, *J. Agr. Food Chem.* **2,** *463 (1954)*). These investigators grew successive crops of red clover, millet, red clover and rye grass on either unlimed or limed Clarksville silt loam with the incorporation of 0.02, 0.05, or 0.1 per cent of a soil-conditioner. This material contained 13.2 per cent sodium, while 36 per cent of its ash was sodium carbonate. Additions of 0.02 per cent of the soil-conditioner did not affect the percentage content of calcium, magnesium, or phosphorus content in the 4 crops. However, 0.05 per cent and 0.1 per cent additions caused decided decreases in the calcium and magnesium content of the crops. In contrast, there were definite increases in the potassium content of the first three crops but not in the rye grass. The additions of soil-conditioner caused progressively greater increases in the sodium content of each of the 4 crops. In another experiment, the effect of 0.05 per cent of the soil-conditioner on 7 different soils was compared with successive crops of red clover and millet. Again the soil-conditioner caused decreases in calcium and magnesium and increases in potassium and sodium content.

Both experiments were conducted in pot cultures so that there was no leaching of the soil comparable to what occurs in the field by natural rainfall. Most likely the reported effects were greater than would have been observed in the field. However, the results indicated clearly that this soil-conditioner induced changes in the concentrations of cations available for incorporation into the plants, which ultimately affected the compo-

sition of these plants. Hence, there needs to be a thorough investigation of the effects of soil-conditioners on plant composition to determine whether or not the ultimate effect is a beneficial or a detrimental one insofar as the use of plant crops for animal and human food is concerned.

It is obvious from these studies that there are numerous ways and means to alter the mineral composition of plants. These are real challenges to the nutritionist to obtain further fundamental data about the requirements of man and animals for various mineral elements in order to be able to define with increasing accuracy the desirable limits of ingestion.

DIETARY FAT AND LIVER NECROSIS

It seems well established now that diets low in the sulfur-containing amino acids, methionine and cystine, and in alpha-tocopherol (vitamin E) lead in due time to the development of acute hepatic necrosis. It involves the development of extensive hemorrhagic areas and the death and disappearance of large numbers of liver cells. This liver disorder differs from the fatty infiltration and diffuse cirrhosis seen under conditions of choline or other methyl donor deficiency.

J. R. McLean and J. M. R. Beveridge (*J. Nutrition* **52,** *499 (1954)*) have reinvestigated the role of dietary fat level in the development of acute massive liver necrosis in the rat. In an earlier paper (*Ibid.* **47,** *41 (1952)*) these same authors reported that diets containing 20, 40 or 70 per cent fat (lard) caused necrotic livers rather rapidly (nineteen to fifty-four days on diet). Diets containing 5 or 10 per cent fat also led to necrosis, but at a later date. On the other hand, feeding a fat-free ration prevented the occurrence of hepatic necrosis in all 5 experimental animals. These animals were observed for one hundred seventy-two days, and the authors considered the possibility that necrosis might have been observed later had the experiment been continued. In the 1954 paper the authors report on the comparision of a fat-free and a 5 to 7 per cent fat diet. These diets were fed to male weanling rats for periods ranging from one hundred four to one hundred seventy-two days. The diagnosis of hepatic necrosis was made on the basis of histologic examination of tissue from the three main lobes of the liver.

The experiment was carried out five times. The first run, taken apparently from the 1952 paper, consisted of 5 animals on the fat-free regimen and 5 on the low-fat diet. All animals receiving fat developed liver necrosis, while the rats on the fat-free ration remained free of pathologic changes. The four subsequent experiments, carried out over a period of fifteen months, showed a consistent high incidence of necrosis. In contrast, the results with the fat-free diet were far from consistent. In the second and third experiments 1 out of 10 and 3 out of 10 animals respectively developed necrotic lesions. In the fourth experiment 8 out of 9 rats showed lesions while in the fifth experiment the incidence decreased to 4 out of 10.

There seems little doubt from these results that the inclusion of a small amount of fat enhances the necrogenicity of diets low in sulfur-containing amino acids and alpha-tocopherol. On the other hand, it is much more difficult to assess the importance of the variability among the several experiments with fat-free rations. The authors rule out seasonal variations as an explanation of their findings. They suggest tentatively that the feeding of a fat-free diet led to changes in the intestinal flora, that these changes were transmitted from one group to the next, and that the altered flora strongly predisposes the animal to the necrogenic action of the diet.

While there is ample evidence of the importance of the intestinal flora in the development of dietary liver necrosis, it is difficult to agree with the authors' explanation of the variability in their experiments. Since it usually requires quite drastic intervention to alter an animal's intestinal flora, it is difficult to see how a modified flora could have been transmitted from one experimental group to another. Some variability may have been introduced by having the animals shipped from a commercial source just prior to the start of each experiment. Many investigators know from experience that the available modes of transportation are likely to be hard on the animals being shipped. It can be concluded, therefore, that the feeding of diets low in sulfur-containing amino acids and in alpha-tocopherol produces a high incidence of liver necrosis if the ration contains at least a small amount of fat. Diets devoid of fat led to a lower incidence of necrosis, ranging in four of these experiments from 0 out of 5 to 4 out of 10. In one experiment the incidence was—perhaps by chance alone—8 out of 9.

In contrast to the observations of McLean and Beveridge, a study by M. Goettsch (*Ann. N. Y. Acad. Sci.* **57,** *839 (1954)*) showed that the incidence of necrotic liver degeneration was not influenced by dietary fat (lard) levels ranging from 0 to 34 per cent. All experimental animals developed the fatal liver pathology. Two major experimental differences may explain the divergent results. McLean and Beveridge used essentially normal weanling male rats from a commercial source while Goettsch maintained a breeding stock on a dietary regimen furnishing minimal quantities of vitamin E and thus obtained offspring with low initial stores of this protective factor. If it is correct to assume that the animals used by McLean and Beveridge possessed greater stores of vitamin E at the start of the experiment, the protective action of a fat-free diet might be demonstrable under such favorable conditions but not under the more drastic regimen employed by Goettsch. Another major difference lies in the composition of the necrogenic diets employed. McLean and Beveridge used a ration in which 18 per cent yeast furnished the dietary protein. Goettsch, on the other hand, made use of low-casein diets.

The study by Goettsch showed that massive hepatic necrosis can be induced by a variety of low vitamin E-low protein diets. The protein sources tested were brewers' yeast, torula yeast, polished rice, red kidney beans and gelatin. An increase in protein or the amino acids cystine or methionine decreased the incidence of necrosis, leading to survival for a considerable period of time. However, the animals eventually displayed the muscular dystrophy and sterility characteristic of vitamin E deficiency. At death the livers were normal. As expected, vitamin E administration also prevented liver necrosis, permitting survival and reproduction. However, the livers showed fatty infiltration and diffuse fibrosis. This was particularly marked when the high fat diets were fed. Excessive fat deposition was prevented by methionine but aggravated by cystine as has been shown repeatedly by the work of others.

K. Schwarz (*Ann. N. Y. Acad. Sci.* **57,** *878 (1954)*) points out, but does not furnish evidence, that animals fed necrosis-producing diets have serious difficulty metabolizing fat. How this observation relates to the necrosis-enhancing effect of fat remains to be established.

APPETITE QUOTIENT AND AD LIBITUM FEEDING

The problem of the proper choice of controls in biologic experiments is a perennial one but often not sufficiently appreciated by various biologists. If ad libitum

feeding is used, it may be debated whether the faster growing animals do so because they eat more or that they eat more because they are growing faster. Although this may seem at first hand to be a "chicken-and-egg" problem, it is of fundamental importance. The first interpretation would imply that the principal effect of the diet was upon the appetite whereas the second would mean that the larger food intake was necessary to meet the demands of the larger body size induced by a more nutritious diet.

Many workers have used the paired-feeding method in which the food intake of a more rapidly growing animal is equalized with that of the less rapidly growing member of the pair. Mitchell in particular has championed this method in the measurement of differences in the nutritive value of proteins. He has carefully considered and discussed the ideal solution (H. H. Mitchell, *Science* **66,** *596 (1927)*; *J. Animal Sci.* **2,** *263 (1942)*) and the limitations of other kinds of feeding tests. He concludes that "*Ad libitum* feeding has no place in a protein nutrition experiment designed to give quantitative data..." Various workers have, however, indicated that the paired-feeding method may not be free from criticism. If the second interpretation given above is correct, it is apparent that the real differences in the diets will be minimized. The larger animal of the pair will require a greater percentage of his diet for maintenance purposes because of his larger size and will thus be penalized. Activity is not ordinarily controlled, and there is no assurance that the 2 animals react similarly in this respect. One animal is fed ad libitum, or nearly so, while the other is starved. Since starvation affects the basal metabolic rate, activity, etc. (A. Keys *et al.*, "The Biology of Human Starvation," *Univ. of Minnesota Press, Minneapolis (1950)*), there is no assurance that equalization of food intakes of necessity equalizes the animal upon a logical basis. Finally, it may be noted that the more restricted animal is hungry most of the time and will consume his food immediately whereas the other member of the pair may eat at will. The time schedule of food intake may well affect the efficiency of food utilization (E. Geiger, *Fed. Proc.* **10,** *670 (1951)*).

The other and less tedious method of attempting to eliminate the effects of food intake is to calculate the "food conversion efficiency" or the gain per gram of food eaten. This would not appear to be a valid method of comparison since as less food is eaten the percentage required for maintenance is increased and efficiency of necessity decreases. D. M. Hegsted and J. Worcester (*J. Nutrition* **33,** *685 (1947)*) found a very close correlation between protein efficiency and rate of growth and concluded upon the basis of a co-variance analysis that gain in weight and protein efficiency measured the same thing. These studies were done with diets containing the same amount of various proteins, 12 per cent, so that the result would hold for food or caloric efficiency as well. Whether the results would be the same in studies of vitamins and other nutrients than proteins remains to be demonstrated but appears likely.

It would appear that the paired-feeding method penalizes the more rapidly growing animal on practically every count that can be suggested. Hence, if differences in the diets are demonstrated by this method, a true difference has probably been shown. On the other hand it is probably fair to say that no "proof" has been advanced to show that paired-feeding equalizes the animals upon a logical or desirable basis. It does not equalize food intake, according to M. Kleiber (*Physiol. Rev.* **27,** *511 (1947)*), who defines equal food intake in animals as being such "that the rate of intake of metabolizable energy is the same multiple of the standard metabolic rate." D. M. Hegsted and V. K. Haffenreffer (*Am. J. Physiol.* **157,** *141 (1949)*) found that in a series of young rats fed diets varying in the amount and kind of protein, the ad libitum

food intake essentially met this condition. The energy intake varied as the mean body weight raised to a power of 0.88 and the results of S. Brody ("Bioenergetics and Growth," *Reinhold Publishing Corp., New York (1945)*) indicated that the basal metabolic rate of rats of the same size also varied with weight to the 0.88 power.

K. J. Carpenter (*J. Nutrition* **51,** *435 (1953)*) has presented a new approach to the problem. Assuming with Kleiber that equal food intake is a rate proportional to body weight$^{0.88}$, Carpenter names this proportion the "appetite quotient," Q_x. Theoretically,

$$\frac{\Delta F}{\Delta t} \times C_x$$

(rate of food consumption) (metabolizable calories per gram of food)

$$= Q_x \times W^{0.88}$$

(body weight).

Since the rate of food intake is variable from day to day, it must be measured over a considerable period of time. Then the

$$\text{(total food eaten) } F \times C_x = Q_x \int_0^T \overline{W^{0.88}}\, dt \text{ and}$$

$$Q_x = \frac{F \times C_x}{\int_0^T W^{0.88}\, dt}.$$

The term $W^{0.88}\, dt$ is simply the area under the curve of $W^{0.88}$ plotted against time.

The data from a previous paper (J. Laguna and K. J. Carpenter, *J. Nutrition* **45,** *21 (1951)*) in which the growth effects of untreated and lime-cooked corn with and without niacin supplements were compared were used to study the "appetite quotients." It may be recalled that growth was seriously depressed by the untreated corn, but this was overcome by either niacin supplementation or lime treatment. The appetite quotient of each animal was calculated in order to compare the mean quotients statistically. No difference in appetite quotient was found. Thus, the animals which grew more slowly on the untreated corn diet consumed food in proportion to $W^{0.88}\, dt$ as did those which grew more rapidly. If the argument of the author is accepted then one must conclude that the poor growth was not due to difference in appetite. It is of some interest that the mean Q obtained in these studies was 0.76 calories per day/$W^{0.88}$. The value obtained by Hegsted and Haffenreffer (*loc. cit.*) by calculation of the regression line of food intake on body weight was practically identical, 0.756, in spite of strain differences in rats, differences in diet, environmental conditions, etc.

This paper thus lends considerable support to the idea that ad libitum feeding is indeed controlled feeding, perhaps upon a more logical basis than can be achieved by the experimenter's manipulation. This is not to say, of course, that either ad libitum or paired feeding should be considered as the ideal or only method suitable for all kinds of studies. Both will continue to be used. The gradual acceptance of the idea that caloric allowances should be based upon basal metabolic rates is indicated by the revised National Research Council Allowances (*see Nutrition Reviews* **12,** *240 (1954)*) which in turn are largely based upon the previous Food and Agriculture Organization recommendations.

MICROORGANISMS AND TOOTH DECAY

Microorganisms have long been suspected to be active agents in the causation of tooth decay. Histologic sections of carious lesions which have been stained by methods designed to detect microorganisms uniformly show that both the softened portion of the lesion itself and surrounding areas of essentially normal tooth substance contain large amounts of bacteria. Much discussion has centered around the type of microor-

ganism observed and the means by which tooth substance is destroyed. Yet there has been little clear-cut evidence to condemn any group of microorganisms as the specific causative agent and no absolute evidence that the microorganisms were anything more than noncontributing contaminants.

A variety of facts has been established in recent years concerning the requirements for foods of specific types of microorganisms in the oral cavity if carious lesions were to develop. Most of these effects have been expected to occur through a bacterial pathway. When a cariogenic diet was introduced into the stomach by tube feeding so that no residues could be retained in the oral cavity, carious lesions did not develop even in desalivated rats (*Nutrition Reviews* **9,** *101* (*1951*)). If only the carbohydrate portion of the same cariogenic diet was introduced into the stomach by tube and the remainder was consumed in normal fashion, a large reduction in carious lesions was observed (J. Haldi, W. Wynn, J. H. Shaw, and R. F. Sognnaes, *J. Nutrition* **49,** *295* (*1953*)). Likewise, in the same report, sucrose was shown to be much less cariogenic when fed in solution than when fed in crystalline form. Furthermore, diets which contained no carbohydrates were incapable of producing carious lesions even in desalivated rats (Shaw, *Ibid.* **53,** *151* (*1954*)). Yet there were circumstances in which two diets contained identical amounts of carbohydrate but had widely different caries-producing potentialities (Wynn, Haldi, Shaw, and Sognnaes, *Ibid.* **50,** *267* (*1953*)). The latter observation is difficult if not impossible to explain on a microbial basis.

In a recent study the "germ-free" technic was used by workers in the Lobund Laboratories at the University of Notre Dame to explore the relation of oral microorganisms to tooth decay (F. J. Orland *et al.*, *J. Dent. Res.* **33,** *147* (*1954*)). The term "germ-free" in these experiments was stated to denote "that special set of circumstances or conditions in which all practical and exhaustive tests fail to demonstrate the presence of viable microorganisms." This involved obtaining rats from a caries-susceptible strain under circumstances which would make them germ-free. Then they had to be isolated throughout the experimental periods within a large, artificial enclosure which served as a mechanical barrier to the external microbic environment. In the early stages of the experiment the rats for these trials were obtained by cesarean section and hand-fed until sufficiently large to be weaned. A total of 13 rats with this background were used for studies of caries initiation and development. In later stages of the experiment, an additional 9 germ-free subjects were obtained from normal deliveries by germ-free females.

The caries-producing ration consisted of: casein, 20 per cent; polished rice (15 to 60 mesh), 60 per cent; cellophane spangles, 3 per cent; salt mixture, 5 per cent; hydrogenated vegetable oil, 5 per cent; yeast extract, 2 per cent; liver powder, 2 per cent; corn oil, 1.6 per cent; and cornstarch, 0.5 per cent, with adequate amounts of the water- and fat-soluble vitamins. This diet was sterilized by steam at 17 pounds per square inch for twenty-five minutes. In addition to this diet the 13 germ-free rats in the early half of the experiment were provided a 5 per cent solution of sucrose ad libitum instead of water. The 9 germ-free rats in the second part were fed only the sterilized diet and water.

A total of 39 control rats was studied which were fed the same sterilized caries-producing diet as the germ-free rats. These controls received either the sucrose solution or water depending on the period during which they were maintained. These were not control rats in the strictest sense of the term for studies on tooth decay, as they were not littermates of the experimental subjects and had experienced widely different experimental and environmental circumstances from the simple absence of microorganisms. However, these rats do

suffice to demonstrate that this particular strain under normal microbial-bearing circumstances does develop carious lesions when fed this sterilized diet.

After suitable periods on the diet, the experimental and control subjects were killed and the incidence of tooth decay was determined by established procedures. None of the 22 germ-free rats showed any evidence of carious lesions, while all but one of the 39 control rats had some evidence of tooth decay. The average number of carious molars for the two groups of control rats was 4.8 and 3.2, respectively. This is incontrovertible evidence that dental caries does not develop in the laboratory rat in the absence of the normal mixed microbial population.

Some interesting data were presented from the Lobund Laboratories on the rates of growth in germ-free rats which have long been awaited. It was stated that the rats taken by cesarean section grew less rapidly when hand-fed than rats nursed by their dams, which is not an unexpected observation in view of the vast number of technical problems involved. In both the group of hand-fed germ-free rats and the group of germ-free rats nursed by germ-free dams, growth was good but possibly not maximal after weaning. The germ-free females at the end of the experimental periods weighed only a few grams less than conventional females from the stock colony. The germ-free males grew appreciably less rapidly than conventional males—for example, the average final weight of 10 combined males with the usual microbial flora was 431 g. at the end of one hundred and seventy days on experiment in contrast to 313 g. after one hundred and seventy-three days on experiment for the 3 germ-free males which had been nursed until weaning by their germ-free mothers. Measurements between certain landmarks also indicated that the germ-free rats had attained somewhat smaller skeletal sizes.

This investigation irrevocably establishes the fact that carious lesions are of bacterial origin and opens up a wide vista for the use of germ-free rats to evaluate the role of different microorganisms in the causation of tooth decay. Through these studies, another link can be forged in the evaluation of the complex process of tooth decay which involves a bacterial vector, an oral environmental influence of foods, a developmental influence of foods, the composition of the teeth, the quantity and type of saliva, as well as the genetic constitution of the subject.

VITAMIN A ACTIVITY OF LARD

The evidence for a possible unidentified substance with vitamin A activity in lard has been previously discussed (H. Kaunitz and C. A. Slanetz, *J. Nutrition* **42,** *375 (1950)*; *Nutrition Reviews* **9,** *165 (1951)*). Kaunitz and Slanetz found that a fraction obtained from lard by molecular distillation at high vacuum contained a significant biologic activity when fed to rats depleted of vitamin A although no vitamin A was detected by the antimony trichloride test and spectrophotometric examination of the unsaponifiable fraction revealed not more than 0.1 microgram of vitamin A per gram. To quote from the review mentioned above, "the authors conclude that the distillate fraction from lard contains a factor with vitamin A-like activity, but which is chemically distinct from vitamin A itself, or from any of the known compounds possessing vitamin A activity. The conclusion appears fully justified by the results reported."

Confirming the earlier reports is the one of J. S. Lowe and R. A. Morton (*Biochem. J.* **55,** *681 (1953)*). They also found that lard failed to give the antimony trichloride test for vitamin A, but demonstrated the oc-

currence of conjugated diene, triene and tetraene acids, compounds in which 2, 3, or 4 carbon-to-carbon double bonds alternate with single bonds. Vitamin A contains this system of alternating single and double bonds. Lowe and Morton succeeded in distilling a lard fraction containing relatively high concentrations of these unsaturated acids.

Animal experiments were carried out as follows. Adult female rats were fed a vitamin A-low diet after mating. The resulting litters when weaned were placed on a diet essentially free of vitamin A. When definite xerophthalmia or marked loss in weight occurred, the animals were divided into two groups, one receiving the vitamin A-free diet plus vitamin A administered orally and the other receiving the vitamin A-free diet supplemented with the lard distillate. The administration of vitamin A brought about an excellent growth response and cured the xerophthalmia. Significant quantities of the vitamin were found in the blood and kidney but none in the liver. The administration of the lard distillate in place of vitamin A also led to an excellent growth response in all animals. Xerophthalmia disappeared in a very short time. However, blood, liver and kidneys contained no demonstrable vitamin A. Administration of 0.6 g. of lard distillate per rat per day elicited a response similar to that of 6 units of vitamin A.

Controverting the conclusion of Lowe and Morton and the previous reports, S. F. Herb, R. W. Riemenschneider, H. Kaunitz, and C. A. Slanetz (*J. Nutrition* **51,** *393 (1953)*) have made careful studies which leave little doubt that the factor with vitamin A activity in the lard fraction is indeed vitamin A itself. Although a great deal of careful work was required, the essence of this paper is that by further fractional distillation and then by chromatographic separation of the unsaponifiable fractions according to the method of J. Boldingh and J. R. Drost (*J. Am. Oil Chem. Soc.* **28,** *480 (1951)*), Herb and co-workers were able to obtain fractions which gave a positive Carr-Price reaction, an absorption curve similar to that of vitamin A, and showed a biologic potency in agreement with that calculated from the absorption at 325 millimicrons. The vitamin A content of lard as determined by biologic assay ranges from 0.4 to 2 units per gram. Direct chromatographic treatment of unsaponifiable material from fresh lard and measurement by spectrophotometric methods yielded a value of 0.4 units per gram, although there was some extraneous absorption in the 300 to 320 millimicron region.

The matter seems firmly settled by the recent report of S. R. Ames and P. L. Harris (*Science* **120,** *391 (1954)*) in which it was shown that the biologic activity of lard distillate is equivalent to its content of vitamin A as measured chemically, and that the characteristic anhydrovitamin A is formed after a dehydration reaction.

Although the final cause for the failure of the previous methods to determine vitamin A is unknown, it was undoubtedly related to relatively large amounts of interfering materials in a low potency product. This is a very common problem in nutrition. The investigator often finds that his methods are reasonably satisfactory when the amounts present are fairly large but become less and less useful as the quantities present decrease. Unfortunately it is often the measurement of small amounts that is of principal interest.

Herb and co-workers refer to some seven papers published during the past two decades in which reference has been made to substances possessing vitamin A activity but assumed to be different from the known vitamin A. The history of the "vitamin A-like substance" in lard provides a good example of the difficulty of proof or disproof of such reports.

NOTES

Inositol in the Seminal Vesicle Secretion of the Boar

Although inositol was discovered over a hundred years ago and has been the subject of considerable nutritional study, its metabolic role has not been established. It is required for the growth of certain yeasts (E. V. Eastcott, *J. Phys. Chem.* **32,** *1094 (1928)*) and for mice (D. W. Woolley, *J. Biol. Chem.* **139,** *29 (1941)*), and a deficiency of this vitamin in hamsters may lead to disturbances in reproduction (J. W. Hamilton and A. G. Hogan, *J. Nutrition* **27,** *213 (1944)*). The lipotropic effect of inositol has been extensively investigated and is demonstrable with careful control of the experimental conditions (*Nutrition Reviews* **9,** *329 (1951)*).

Animal tissues which have been studied previously contain only very small amounts of free inositol. The bound forms include phospholipids and a water-soluble non-dialyzable inositol complex (Woolley, *loc. cit.*). T. Mann (*Proc. Roy. Soc. (London) B* **142,** *21 (1954)*) has reported the occurrence of relatively enormous quantities of free inositol in the seminal vesicle secretion of the boar. The fluid was obtained from the seminal vesicles of boars of various ages and inositol was isolated from the deproteinized material in pure chemical form. Inositol was present to the extent of from 2 to 3 g. per 100 ml. of fluid. This represents approximately 20 per cent of the dry weight and 40 to 70 per cent of the dialyzable dry weight of seminal fluid. The concentration of inositol in the seminal fluid of the boar is about twenty times greater than any previously reported concentration of the vitamin in animal or plant materials. The other major constituents of the seminal fluid were found to be ergothioneine, fructose, and citric acid. Sodium chloride was present in very low concentration. Attempts were made to relate inositol to the metabolism of sperm cells, but there was no effect on the rate of anaerobic fructolysis or on the motility of the cells. The author speculates that inositol may function in maintaining osmotic pressure of the seminal fluid.

Although the significance of this high concentration of inositol in the seminal fluid of the boar is obscure, it is of interest, and a study of the effect of inositol deficiency in pigs on the production and motility of sperm cells would be an interesting extension of the finding.

Effect of Climatic Factors on Vitamin Content of Plants

Various workers have shown that climate and seasons influence the vitamin content of green plants. Both light intensity and temperature are important factors. Still, these two factors do not completely account for the relatively high vitamin content of plants during the summer months. Several workers who have studied tomatoes and cowpeas for ascorbic acid content, and tomatoes and cabbage for thiamine content, found that longer days (photoperiods) were conducive to higher vitamin contents. F. G. Gustafson at the California Institute of Technology (*Am. J. Bot.* **40,** *256 (1953)*) has studied this problem with peas, beans and tomatoes with regard to their content of thiamine, riboflavin and niacin. Only the green parts of plants were studied. Plants were depleted by a dark treatment before use of the experimental conditions.

Temperature conditions were 6°, 14°, 20°, and 26° C. Photoperiods were eight, sixteen, and twenty-four hours. Twelve combinations of temperatures and photoperiods were employed. As for thiamine content, it appears that if the length of day has any effect at all, a long day is more likely to cause a decrease than an increase. Plants grew more in the longer photoperiods; thiamine content is not known to be directly related to growth.

At the three higher temperatures, whenever differences occurred, continuous light led to highest riboflavin content. At 6° C. very irregular results were obtained. When plants were first starved the longest photoperiod always gave the highest riboflavin content. Here growth is definitely associated with riboflavin content.

Niacin content increased progressively with increase of day length, in peas. In tomatoes the increase was slight, especially at higher temperatures. Beans had higher niacin contents at longer photoperiods in general, but more particularly at higher temperatures.

These findings are of interest in plant physiology and may have practical significance for vegetables grown in greenhouses for high-priced markets. Knowledge on these points could lead to better choice of materials for freezing, canning, etc. It is not likely to alter the more usual outdoor type of vegetable raising. Extremes of day length would of course exist between northern and southern regions. Most effects of these environmental conditions are relatively small compared to losses due to storage, mishandling, cooking, and other treatments received before reaching the consumer's table.

CLINICAL NUTRITION BRIEFS

"The above-described findings provide some insight into the possible defects involved in the etiology of hepatolenticular degeneration. These observations illustrate the familial nature of the defect in amino acid metabolism, which appears to precede the development of both the hepatic and the lenticular degeneration. The chronic nutritional drain resulting from the persistent aminoaciduria may well explain the development of hepatic cirrhosis." (*Nutrition Reviews* **12,** *198* (*1954*), Copper and Amino Acids in Wilson's Disease.)

"As a result of their two years experience with this kind of therapy, the authors conclude that vitamins are not generally effective in the treatment of alcoholism. However, the cases which maintained improvement while under vitamin therapy are of considerable interest." (*Nutrition Reviews* **12,** *202* (*1954*), Vitamin Treatment of Alcoholism.)

"Fructose administration has been recommended by others for the treatment of diabetic ketosis. The work reported by Rosecan and Daughaday supports this advice, but as they point out 'insulin is necessary for the full anti-ketogenic effect.' That is, in the absence of insulin there was conversion of fructose to glucose, a subsequent rise in blood sugar and a markedly diminished tissue uptake of sugar." (*Nutrition Reviews* **12,** *227* (*1954*), Carbohydrate in the Treatment of Diabetic Ketosis.)

"The data did suggest that the incorporation of the single dose of acetate into cholesterol was complete after 0.3 day. Cholesterol, both free and ester, in the plasma was synthesized in man from orally administered C^{14}-labeled sodium acetate, approximately 3 per cent of the administered acetate being incorporated." (*Nutrition Reviews* **12,** *230* (*1954*), Cholesterol Synthesis in Man.)

"The Vipeholm data point with vigor to the definitely greater importance of the physical form in which sugars are ingested than the total amount consumed. These data also emphasize the real importance of the several constitutional factors which determine caries-susceptibility and the difficulty with which these factors are overruled by unfavorable oral environmental circumstances." (*Nutrition Reviews* **12,** *233* (*1954*), Dental Decay and Carbohydrates.)